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Critical Capillary Oxygen Partial Pressure and Lactate Threshold in Patients With Cardiovascular Disease

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Objectives. The aim of this study was to determine the relation between femoral vein oxygen partial pressure (Po_2) and lactate increase during exercise in patients with cardiovascular disease.

Background. Considerable controversy surrounds the relation between the increase in lactate during exercise and the oxygen supply to the exercising muscles. We assumed that femoral vein Po_2 would be a measure of end-capillary Po_2 during leg-cycling exercise and that it would decrease to a "floor" level when the critical capillary Po_2 (the Po_2 below which the capillary-mitochondrial difference would be too low to allow oxygen consumption) was reached. At the critical capillary Po_2, anaerobic metabolism should take place, and lactate should increase in the effluent blood.

Methods. Ten patients with cardiovascular disease performed two 6-min constant work rate tests (moderate and heavy intensity) and an incremental exercise test to the symptom-limited maximum on a cycle ergometer. Femoral vein blood was repeatedly sampled through a percutaneous catheter before and during each exercise test.

Results. The Po_2 rapidly decreased toward a minimal value with increasing oxygen uptake for all three tests in all patients. After reaching its nadir (18.2 ± 2.0 mm Hg), the Po_2 remained unchanged in five patients but increased in the other five patients despite the further increase in work rate and oxygen uptake. The relation between Po_2 and oxygen uptake was characteristic for each patient and independent of the protocol used for the study. Femoral vein lactate did not change appreciably until Po_2 reached the minimal (critical) value. Thereafter, it dramatically increased without a further decrease in Po_2. The minimal Po_2 was positively correlated with the peak oxygen uptake ($r = 0.70$, $p = 0.01$).

Conclusions. During leg-cycling exercise, muscle capillary Po_2 reaches a minimal value in the midrange of the subjects' work capacity before lactate concentration increases in patients with cardiovascular disease. The lack of further decrease in Po_2 at the oxygen uptake at which lactate starts to increase suggests that the minimal capillary Po_2 is the "critical" capillary Po_2.

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Considerable controversy surrounds the relation between oxygen supply to the tissues and the increase in lactate (1,2). The controversy, however, is not the result of a dispute over experimental data; rather, it concerns the reliance on information derived from techniques that only indirectly address the question of the importance of the oxygen supply/requirement balance during exercise and net lactate production (lactate concentration increase).

Muscle surface fluorescence analysis of reduced nicotinamide adenine dinucleotide (NADH) (3) and muscle oxygen partial pressure (Po_2) estimated from oxymyoglobin saturation (4) have been used to suggest that net muscle lactate production during exercise is independent of the oxygen supply to the muscle. It needs to be recognized, however, that these techniques measure global (average) muscle concentrations of NADH or oxymyoglobin saturation, respectively, on the surface muscle. Because the capillary Po_2 is heterogeneous, decreasing from ~90 mm Hg on the arterial side to a value that is above or at the critical capillary Po_2 on the venous end (Fig. 1) (5), techniques that reflect the global tissue Po_2 may not reliably determine whether a critical capillary Po_2 (which, by definition, is the lowest capillary Po_2) is reached when net lactate production increases. Below the critical capillary Po_2, estimated to be between 15 and 20 mm Hg by Wittenberg and Wittenberg (6), the diffusion gradient of oxygen would be inadequate to sustain mitochondrial respiration.

Because the increase in blood flow is about six times the increase in oxygen uptake during exercise, and 6 liters of blood (assuming a hemoglobin concentration of 15 g/dl) has ~1.2 liters of oxygen during air breathing at sea level, only about one-sixth of the oxygen entering the capillary bed would be left at the venous end of the capillary. This brings the end-capillary Po_2 into the range of the critical capillary Po_2, as shown in Fig. 1.

The critical capillary Po_2 during exercise, therefore,

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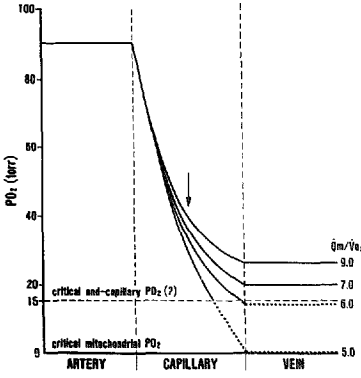

Figure 1. Model of muscle capillary oxygen partial pressure (Po_2) along a representative muscle capillary during exercise that would provide the end-capillary (femoral vein) Po_2 shown. The model assumes a hemoglobin concentration of 15 g/dl, arterial Po_2 of 90 mm Hg, and muscle oxygen uptake ($\dot{V}o_2m$) of 1 liter/min (corresponding to an adult walking at 3 mph or 5 km/h). Curves are contours of Po_2 along the capillary for various muscle perfusion ($\dot{Q}m$) to $\dot{V}o_2m$ ratios. The Po_2 of each curve is calculated on the basis of the oxyhemoglobin dissociation curve (11) as blood oxygen content decreases according to its $\dot{Q}m/\dot{V}o_2m$ ratio, assuming a Bohr effect dependent only on the respiratory component and linear oxygen extraction along the capillary (Krogh model). The curve for a $\dot{Q}m/\dot{V}o_2m$ = 5, which decreases to zero, is dashed below the critical capillary Po_2 to indicate that this could only occur if no diffusion barrier between red cell and mitochondrion existed. Note that end-capillary Po_2 is affected more than midcapillary Po_2 (arrow) as $\dot{Q}m/\dot{V}o_2m$ is varied.

should be the "floor" or lowest Po_2 value achievable during exercise despite increasing work rate. When the critical capillary Po_2 is reached, not only should end-capillary and therefore femoral vein Po_2 reach its nadir or "floor," but anaerobic production of adenosine triphosphate should start, and lactate should accumulate (net increase in lactic acid production). In patients with cardiovascular failure, end-capillary Po_2 during exercise would probably reach a critical level, as a result of inadequate blood flow to the working muscles, at a lower work rate than in normal subjects. The lower the level of critical capillary Po_2, the lower might be the exercise capacity, reflecting the severity of heart disease in these patients.

This study was designed to ascertain whether the critical capillary Po_2 is reached before the subject's maximal oxygen uptake and to determine the relation between lactate increase and the critical capillary Po_2 in patients with cardiovascular disease.

Table 1. Physical Characteristics, Work Rates of Moderate and Heavy Intensity Studied and Cardiac Diagnosis for Each Patient

Pt No./ Gender	Age (yr)	Height (cm)	Weight (kg)	Constant Work Rate (W)		Cardiac Diagnosis
				Moderate	Heavy	
1/M	74	162	55	40	87	HHD
2/M	60	160	52	32	61	ASR
3/M	63	153	54	47	84	CAD
4/M	72	165	61	50	92	HHD
5/M	67	163	55	64	110	HHD
6/M	72	160	62	53	94	CAD
7/M	46	171	79	85	148	CAD
8/M	71	160	60	38	71	MR
9/F	55	154	57	36	70	DCM
10/F	57	155	52	31	58	MSR, AR
Mean	63.7	160.3	59.7	47.6	87.5	
SD	8.7	5.2	7.7	15.8	25.3	

AR = aortic regurgitation; ASR = aortic stenoregurgitation; CAD = coronary artery disease; DCM = dilated cardiomyopathy; HHD = hypertensive heart disease; MR = mitral regurgitation; MSR = mitral stenoregurgitation; Pt = patient.

Methods

Study patients. We studied 10 patients (eight men, two women, 46 to 74 years old) with cardiovascular disease at Kasumigaura Branch Hospital, Tokyo Medical and Dental University (Table 1). On the study day, all the patients were in sinus rhythm. Medications were withheld for 48 h before the study. The nature and purpose of the study and the risks involved were explained to each patient before his or her voluntary informed consent was obtained.

Exercise protocol. An upright, electromagnetically braked cycle ergometer (Siemens-Elema 930, Siemens Elema AB) was used for exercise tests. Before the study, all patients performed a symptom-limited incremental exercise test to determine peak oxygen uptake and oxygen uptake at the lactic acidosis (anaerobic) threshold (5,7–10); this was done noninvasively by respiratory gas analysis. Two 6-min constant work rate tests, one of moderate and one of heavy intensity, and an incremental (ramp pattern) exercise test to the symptom-limited maximum were performed by each patient on the study day. Patients rested for ~60 min between tests. Heart rate and a 12-lead electrocardiogram were monitored throughout the test by System ML-5000 (Fukuda Denshi Co.).

Constant work rate test. The work rates selected as moderate and heavy work intensities for each subject were determined from the preliminary incremental exercise test. The moderate-intensity work rate corresponded to oxygen uptake at 80% of the lactic acidosis threshold. For heavy-intensity exercise, the difference between the work rate at the lactic acidosis threshold and that at peak exercise was first calculated; the work rate of heavy-intensity exercise was then determined by adding 50% of this difference to the work rate at the lactic acidosis threshold.

Incremental exercise test. The incremental (ramp) exercise test consisted of cycling at 60 rpm on the ergometer for

Table 2. Variables of Exercise Capacity, Oxygen Partial Pressure and Femoral Vein Lactate Concentration Determined During the Incremental Exercise Test

Pt No.	Maximal Work Rate (W)	LAT (ml/min per kg)	Peak $\dot{V}o_2$ (ml/min per kg)	Po_2 (mm Hg)			Lactate Conc (mmol/liter)	
				Rest	Minimal	Peak Exercise	Rest	Peak Exercise
1	125	14.9	22.3	22.7	20.2	29.6	0.8	5.4
2	85	11.5	17.4	26.6	14.4	14.4	0.8	2.9
3	117	15.7	22.4	24.0	19.6	19.8	0.8	4.7
4	133	12.7	21.8	31.9	20.5	23.0	0.6	4.8
5	143	12.4	21.2	21.7	17.4	28.9	1.1	5.8
6	127	11.3	18.7	25.8	19.5	25.6	0.9	4.3
7	182	11.9	23.5	23.1	18.8	22.7	0.7	6.5
8	110	10.2	17.0	22.3	16.4	23.7	0.7	4.1
9	100	10.8	16.7	22.7	15.6	18.4	0.9	3.8
10	87	11.4	18.7	21.3	19.5	23.6	0.9	3.6
Mean	120.9	12.3	20.0	24.2	18.2	23.0	0.8	4.6
SD	27.3	1.7	2.4	3.0	2.0	4.4	0.1	1.0

Conc = concentration; LAT = lactic acidosis threshold determined by the respiratory gas analysis; Po_2 = oxygen partial pressure; Pt = patient; $\dot{V}o_2$ = oxygen uptake.

3 min at 20 W and then progressively increasing work rate at 1 W every 6 s.

Measurements of lactate and blood gases during exercise. Femoral vein blood was obtained before and during exercise from a 16-G polyvinyl chloride catheter (Intramedicut Catheter Kit, Nippon Sherwood Medical Industries Ltd.), which was inserted into the femoral vein 2 to 3 cm below the inguinal ligament and advanced ~8 cm proximally. For the constant work rate tests, blood was sampled before and at 0.5, 1, 2, 4 and 6 min during exercise. For the incremental exercise test, it was sampled before, at 3 min of 20-W cycling and every 1 min during the incremental exercise period. Blood gases were measured within 3 min after sampling by an automatic blood gas analyzer (GASTAT-1, Techno Medica Co. Ltd.) for pH, bicarbonate, carbon dioxide partial pressure (Pco_2) and Po_2, and a lactate analyzer (model 2300 STAT, YSI Inc.) determined lactate concentration. Femoral vein oxygen saturation (So_2) was calculated using the following equations (11):

$$So_2\,(\%) = \frac{(Po_2')^3 + 150\,Po_2'}{(Po_2')^3 + 150\,Po_2' + 23{,}400} \times 100, \quad [1]$$

where

$$Po_2' = Po_2 \times 10^{[0.48(pH - 7.40) - 0.001\,3([HCO_3^-] - 25)]}. \quad [2]$$

Respiratory gas analysis during exercise. Oxygen uptake, carbon dioxide output and the rate of respiratory air flow were measured at rest and throughout the exercise period using an Aeromonitor AE-280 (Minato Medical Science). This system consists of a hot-wire flow meter and oxygen and carbon dioxide gas analyzers (zirconium element-based oxygen analyzer and infrared carbon dioxide analyzer). Gas was sampled at a rate of 220 ml/min through a filter by a suction pump through the analyzers. The system was calibrated before each study. Oxygen uptake and carbon dioxide output were corrected to standard conditions, and average values, determined by interpolation, were calculated every 10 s.

Peak oxygen uptake was defined as the highest oxygen uptake attained during the incremental exercise test. Oxygen uptake at the lactic acidosis threshold was also determined from the incremental exercise test performed on the study day, noninvasively by respiratory gas analysis using the V-slope method (7,8).

Statistical analysis. All data are reported as mean values ± SD. Linear regression analysis was used to correlate the minimal Po_2 with peak oxygen uptake and the lactic acidosis threshold. Differences were considered significant at the $p < 0.05$ level.

Results

Variables of exercise capacity are shown in Table 2. The average values for the maximal work rate, lactic acidosis threshold and peak oxygen uptake, determined from the incremental exercise tests, were 120.9 ± 27.3 W, 12.3 ± 1.7 ml/min per kg and 20.0 ± 2.4 ml/min per kg, respectively. In Figure 2, femoral vein Po_2 is plotted as a function of oxygen uptake for each exercise test for each patient. Femoral vein Po_2 rapidly decreased toward a minimal value with increasing oxygen uptake for all three tests in all 10 subjects studied. After reaching its nadir (mean [±SD] 18.2 ± 2.0 mm Hg), Po_2 remained unchanged in five patients (Patients 2, 3, 4, 9, 10) and increased in the other five patients (Patients 1, 5, 6, 7, 8) despite the further increase in oxygen uptake. The relation between Po_2 and oxygen uptake was characteristic of the patient and unaffected by the exercise protocol. The finding that a "floor" value in Po_2 is

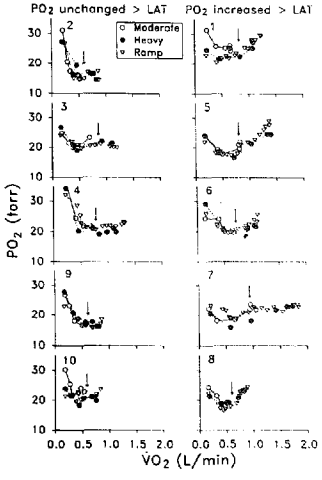

Figure 2. Femoral vein oxygen partial pressure (Po_2) plotted as a function of oxygen uptake ($\dot{V}o_2$) during two constant work rate tests of moderate and heavy intensity and an incremental (ramp) exercise test for each patient. Numbers correspond to patients in Tables 1 and 2. Femoral vein Po_2 rapidly decreased toward a minimal value with increasing $\dot{V}o_2$. After the femoral vein Po_2 reached its nadir, it increased in five patients despite increasing $\dot{V}o_2$ (right column) but was unchanged for the other five patients (left column). Arrows show the lactic acidosis threshold (LAT) determined noninvasively by the V-slope method during the incremental exercise test.

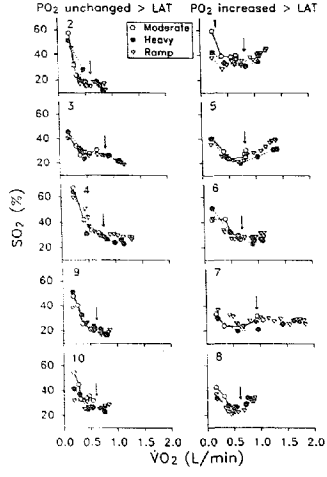

Figure 3. Femoral vein oxygen saturation (So_2) plotted as a function of oxygen uptake ($\dot{V}o_2$) for each exercise test for each patient. Arrows show the lactic acidosis threshold (LAT) determined by the V-slope method during the incremental exercise test. The So_2 was calculated using equations 1 and 2 (see text). Po_2 = femoral vein oxygen partial pressure.

achieved at a submaximal work rate is consistent with the critical capillary Po_2 concept. The critical capillary Po_2 of 18.2 ± 2.0 mm Hg found in this study is in remarkably close agreement with that calculated by Wittenberg and Wittenberg (6).

In three of the patients (Patients 4, 9, 10), Po_2 increased at the very highest work rate for the incremental exercise test only. This appears to be primarily due to the Bohr effect resulting from an increase in net lactic acid production because the calculated So_2 did not increase (Fig. 3), in contrast to the five patients (Patients 1, 5, 6, 7, 8) with increased Po_2 at the lactic acidosis threshold.

Femoral vein lactate did not change appreciably until Po_2 reached the minimal value (Fig. 4). Thereafter, it dramatically increased with no further decrease in Po_2. Thus, lactate increases at a threshold femoral vein (end-capillary) Po_2. After reaching the minimal value, Po_2 was unchanged, whereas lactate increased in five patients (Patients 2, 3, 4, 9, 10). In contrast, Po_2 increased in the other five patients (Patients 1, 5, 6, 7, 8). No subject's Po_2 decreased further after lactate started to increase.

Figure 5 shows the relation between the minimal femoral vein Po_2 obtained during the incremental exercise test and the peak oxygen uptake and lactic acidosis threshold measured by the V-slope method. The minimal Po_2 was positively correlated with the peak oxygen uptake ($r = 0.70$, $p = 0.01$) and lactic acidosis threshold ($r = 0.57$, $p = 0.04$).

Discussion

Concept of critical capillary Po_2. The concept of the critical capillary Po_2 was explored in patients with cardiovascular disease. Femoral vein Po_2 was found to decrease with increasing work rate until it achieved a minimal value. Then it remained constant or increased but did not decrease further. This minimal value must reflect the critical capillary Po_2. It was attained at a submaximal oxygen uptake, at or below the lactic acidosis threshold estimated by the V-slope gas-exchange method (Fig. 2). The values ranged between 14.4 and 20.5 mm Hg, depending on the subject. Femoral vein Po_2 was stable or increased despite the increasing

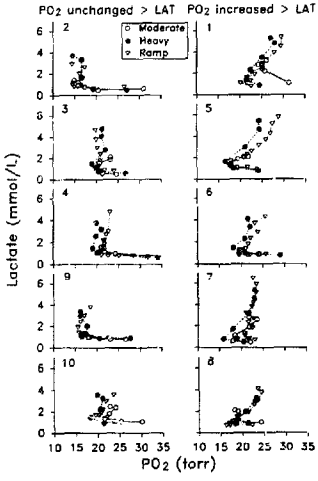

Figure 4. Relation between femoral vein lactate and oxygen partial pressure (Po_2) for each exercise test for each patient. Femoral vein lactate dramatically increased after Po_2 reached its smallest value. After reaching the minimum, Po_2 was unchanged in five patients (**left column**) but increased in the other five patients (**right column**). LAT = lactic acidosis threshold determined by the V-slope method.

metabolic demand. The same minimal Po_2 was reached during progressively increasing and constant workrate exercise tests (Fig. 2). Because femoral vein Po_2 reflects the end-capillary Po_2, its failure to decrease further and the subsequent increase in lactate suggest that the minimal femoral vein Po_2 is the critical capillary Po_2.

The Po_2 at which lactate increased was reproducible and independent of the work rate protocol for a given patient (Fig. 4). The pattern of change and reproducibility of the responses for a given subject provide strong support for the hypothesis that net lactate production increases during exercise after the critical capillary Po_2 has been reached.

The minimal (critical) Po_2 was significantly related to exercise capacity, as measured by the peak oxygen uptake and lactic acidosis threshold variables (Fig. 5). The observation that the critical capillary Po_2 was higher with a higher work capacity possibly reflects the higher capillary-mitochondrial Po_2 gradient needed for diffusion when oxygen consumption is high in these patients.

Mechanisms of an increase in Po_2 during exercise. The mechanisms underlying the unexpected finding of an increase in femoral vein Po_2 after it had reached its minimal value in 5 of 10 patients (Patients 1, 5, 6, 7, 8) is of considerable interest. A rightward shift in the oxyhemoglobin dissociation curve might explain a small part of the increase, but it could not explain the increase in the calculated (from Po_2, pH and HCO_3^-) So_2 (11) with increasing oxygen uptake, as was found in this study (Fig. 3). Because arterial oxygen content would not be increasing under the conditions of this study, the increase in Po_2 in five patients may be the result of increased blood flow relative to the increase in oxygen uptake.

An explanation for the increase in blood flow leading to increases in femoral vein Po_2 and So_2 above the threshold is that these patients might have uneven muscle blood flow ($\dot{Q}m$) relative to muscle oxygen consumption ($\dot{V}o_2m$). With increasing oxygen requirement, it would be necessary to increase blood flow. But as blood flow increased, the low-$\dot{Q}m/\dot{V}o_2m$ muscle units could not contribute as much to the increase in flow requirement as the high $\dot{Q}m/\dot{V}o_2m$ units. From Figure 1, it is evident that as oxygen uptake increases during exercise, the low $\dot{Q}m/\dot{V}o_2m$ muscle units should contribute less to the oxygen uptake than the high $\dot{Q}m/\dot{V}o_2m$ units because the critical capillary Po_2 is reached earlier in these capillaries. Because the high $\dot{Q}m/\dot{V}o_2m$ units have a

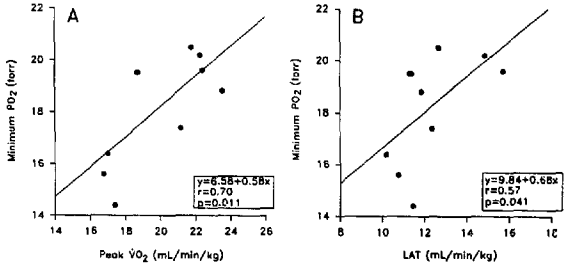

Figure 5. Relation between the minimal femoral vein oxygen partial pressure (Po_2) obtained during the incremental exercise test and the peak oxygen uptake ($\dot{V}o_2$) (**A**) and the lactic acidosis threshold (LAT) determined by the V-slope method (**B**). The minimal Po_2 was significantly correlated with the peak $\dot{V}o_2$ and the lactic acidosis threshold.

higher end-capillary Po_2 than the low $\dot{Q}m/\dot{V}o_2m$ units, when the former make a progressively greater contribution to the total blood flow to the leg, the mixed femoral venous Po_2 should increase. Thus, after the critical capillary Po_2 had been reached, an increasing Po_2 and So_2 may reflect a progressively greater contribution of the high $\dot{Q}m/\dot{V}o_2m$ to the overall metabolic rate. In contrast, lactate concentration would increase in the low $\dot{Q}m/\dot{V}o_2m$ muscle units. The mechanism of regional control of the $\dot{Q}m/\dot{V}o_2m$ units is not well understood.

Influence of exercise protocol on Po_2 and lactate. The levels of femoral vein Po_2 and So_2 and lactate changes during heavy-intensity constant work rate exercise were similar to those obtained for the progressively increasing work rate (ramp) exercise test for each subject when related to oxygen uptake. This suggests a fundamental relation among oxygen consumption, Po_2 and net lactate production. The finding that femoral vein lactate increases when end-capillary Po_2 reaches a minimal value is consistent with the concept that muscle capillary Po_2 reaches a critical value at the lactate threshold. The fact that this occurs in the midrange of the subject's work capacity, well below maximal oxygen uptake, differs from the assumptions made in the review by Connett et al. (12), which suggests no oxygen flow limitation until maximal oxygen uptake has been reached.

Because the exercise protocol did not affect the femoral vein Po_2 at which lactate increased, net lactate production (accumulation) appears to depend on tissue oxygenation, not on work rate or protocol. Although this study was performed in patients with a variety of cardiovascular diseases, the consistent findings in 30 experiments performed with 10 subjects, using different protocols, suggest that the observation of a critical capillary Po_2 being reached before lactate concentration increases in a general phenomenon related to the oxygen requirement. Stringer et al. (13) made similar observations supporting the concept of a critical capillary Po_2 being reached during progressively increasing and constant work rate exercise before lactate concentration increases in normal men.

Critical capillary Po_2 in patients with cardiovascular disease. Muscle biopsy studies are consistent with a modest reduction in the activity of aerobic enzymes of the tricarboxylic acid cycle in patients with chronic heart failure (14,15). Thus, it has been inferred that skeletal muscle biochemistry is altered in patients with long-term heart failure. However, it is not clear whether the decrease in aerobic enzymes of the tricarboxylic acid cycle is due to physical inactivity or is part of the primary disease in these patients.

Minimal femoral vein Po_2 during incremental exercise has been reported to be ~18 mm Hg in normal subjects (13). The observations reported here showing that 1) the lower the minimal end-capillary Po_2, the lower the peak oxygen uptake of the patient (Fig. 5), and 2) the end-capillary Po_2 decreases to similar critical values in patients with cardiovascular disease as in normal subjects (13) argue against a skeletal muscle aerobic (tricarboxylic acid cycle) enzyme deficit being a primary disturbance in our patients. If this were the primary defect, the critical capillary Po_2 would be higher than normal, and higher rather than lower, the more limited the patient. A defect in the tricarboxylic acid cycle enzymes should reduce the flow of reducing equivalents to the electron transport chain, thereby reducing the rate of oxygen utilization. Thus, detailed measurements of critical capillary Po_2 are needed in patients with heart failure to distinguish between a primary defect in tricarboxylic acid cycle aerobic enzymes in skeletal muscle and a defect in oxygen transport to the muscle.

Study limitations. Several other factors have to be considered to interpret the observed relation between the increase in lactate and the decrease in Po_2. We obtained blood from a catheter that was inserted into the femoral vein 2 to 3 cm below the inguinal ligament and advanced 8 cm proximally. This site of sampling might have influenced the Po_2 and lactate levels in the present study.

Although increased blood lactate reflects a lactate increase in the contracting muscles, blood lactate is determined both by lactate production in the muscles and by lactate release into the blood (16). The amount of lactate release must depend on the blood flow through muscles and on the arterial-venous lactate difference. In this study, we did not measure the arterial lactate concentration, and therefore we cannot measure lactate balance. We focused this study on the change in Po_2 in end-capillary blood to determine the critical capillary Po_2 and its relation to muscle lactate increase and $\dot{V}o_2$.

It is clear from lactate balance measurements across the exercising extremity that lactate is produced by the exercising muscle when femoral vein and arterial lactate increase (17). It has been suggested, however, that lactate production and metabolism occur during exercise in other tissues or organs, such as the liver (18). Thus, liver function might influence blood lactate concentration. No patient had liver disease in the present study.

Conclusions. In the present study, the relation between oxygen uptake and end-capillary (determined from femoral vein blood) Po_2 and lactate during leg-cycling exercise were found to support the concept that muscle capillary Po_2 reaches a critical value before maximal oxygen uptake and before net lactate production increases (lactate accumulation). The critical capillary Po_2 was found to be 14 to 21 mm Hg in the subjects participating in these studies. This is in agreement with the critical capillary Po_2 calculated by Wittenberg and Wittenberg (6). The critical capillary Po_2 did not vary with the exercise protocol in a given subject. The fact that lactate concentration did not increase significantly until the critical capillary Po_2 had been reached supports the concept that the lactate threshold identifies the oxygen uptake at which the critical capillary Po_2 is reached and above which anaerobic metabolism contributes to muscle bioenergeti

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